REMARKS

Reconsideration and allowance of the subject application are requested.

Claim 28 is amended above to specify that the claimed composition confers protective immunity against Hantavirus infection. Support for this revision is found throughout the original disclosure, for instance, at page 4, line 13 – page 5, line 27, and the examples section. No new matter is introduced by this amendatory language, nor are new issues raised for the Examiner's consideration since compositions that confers protective immunity against Hantavirus infection (such as vaccines and the like) have been the subject of our invention and the Examiner's examination from the beginning of prosecution. Entry into the record of the amended claim is requested.

In the November 4 Office Action, the Examiner indicated that the subject matter of claims 33, 34, 42, 43, 50 and 51 is allowable.

However, claims 28-32, 35-41, 44, 45, 48 and 49 are rejected under 35 U.S.C. §103(a), as obvious over the combination of the following five references: (1) Schmaljohn (Rev. Med. Virol., 4:185-196, 1994); (2) Chu et al., (J. Virol., 69(10):6417-6423, 10/95); (3) Arikawa et al., (Virol, 176:114-125, 1990); (4) Montgomery et al., (Pharmacol. Ther., 74(2):195-205, 1997); and (5) Donnelly et al., (Ann. Rev. Immunol., 15:617-648, 1997). We respectfully disagree with the Examiner for the following reasons.

In response to our Amendment filed August 16, 2002, the Examiner first stated that independent claim 28 does not specifically recite a "vaccine", but a "composition", which is allegedly not commensurate in scope with the arguments we presented in that Amendment. Hence, we have amended this claim to recite that the composition confers protective immunity against Hantavirus infection. This makes the effectiveness of the composition to confer protective immunity a necessary requirement. We ask that our arguments in the August 16, 2002 Amendment be considered again light of this.

We have carefully reviewed the Examiner's position as set forth in this Office Action and the previous one. One significant problem appears to be that the Montgomery et al. and Donnelly et al. references are being interpreted as teaching that DNA vaccines are obvious based on the success of vaccinia vaccine, combined with the success of the present inventors in Schmaljohn et al. showing that the genes expressed by vaccinia virus

were immunogenic. Although we agree with the Examiner that Donnelly and Montgomery teach that DNA vaccines are easier to use, more flexible and safer than vaccinia vectored vaccines, there is **no teaching in any of the references that vaccinia virus vaccines predict efficacy of DNA vaccines**. This is not suggested by Schmaljohn et al. or in Arikawa et al. (We note again in this Amendment that Arikawa has little to do with DNA vaccines, or really any vaccines.)

The combined teachings do not—indeed, cannot—show that one can extrapolate vaccinia virus results to DNA vaccines for a couple of reasons.

(1) Vaccinia virus replicates only in a host cell cytoplasm. This is well known in this area of art. The RNA transcripts produced by a recombinant vaccinia virus, therefore, are not subject to host cell modifications that occur exclusively in the nucleus of a mammalian cell, in particular, RNA splicing. Because DNA vaccines must be transcribed by host cell polymerase in a mammalian nucleus, cryptic splice sites, which are not problems for the natural RNA virus, or for transcripts produced by vaccinia virus, could pose significant problems for transcripts produced by a DNA vaccine plasmid. Hantaan virus has cryptic splice sites that can be predicted by computer modeling, so it can be predicted that the DNA vaccine would not work, rather than that it would work.

(2) Our novel composition is a necessary requirement for the effectiveness of protective immunity against Hantavirus infection. With the ballistic delivery method that we use, it is essential that the plasmid on the inert particle be delivered directly to the nucleus. DNA delivered to the cytoplasm does not move to the nucleus, and therefore no antigens are produced. Consequently, our specific composition including the inert particle and the DNA, and its specific method of use, are critical to the effectiveness of the method.

(3) We disagree with the Examiner's assertion on page 3 of the Office Action that "the claims are broadly drawn to any polynucleotide operative in a mammalian cell and does not exclude the use of any particular vector as long as it is functional in a mammalian cell". Again, the reasons are that host cell polymerase III must recognize the promoter (for instance, in one of our preferred embodiments, the CMV promoter) and that can only occur in the nucleus of the cell. In contrast, as is well known, vaccinia virus

carries its own polymerase into the cell and uses that to make the RNA transcripts in the cytoplasm of the cell.

In summary, it only becomes "obvious" that a DNA vaccine will work AFTER it is shown that (1) the DNA can get into the nucleus (i.e., using our novel composition); (2) the DNA can be transcribed to yield intact mRNA in the nucleus; (3) the RNA transcripts can get out of the nucleus and move to the cytoplasm where they can be translated to the antigen.

We reiterate that vaccinia is a live virus and is used to infect host cells. Immune responses to vaccinia virus are greater than the responses to the foreign gene expression product that the vaccinia virus produces. Because vaccinia virus stimulates strong cell-mediated immune responses, whereas Hantaan virus does not, the type of immune response generated is different than is elicited by a DNA vaccine. Thus, it is would have been unreasonable for someone having ordinary skill in this area of art to use vaccinia vaccine technology as taught by Schmaljohn, Chu or Arikawa in combination with Montgomery or Donnelly to achieve our claimed DNA vaccine compositions.

The disclosures of Schmaljohn, Chu and Arikawa would not have lead someone to combine these references with Montgomery and Donnelly to arrive at the DNA vaccine compositions of our invention.

Therefore, we submit that none of claims 28-32, 35-41, 44, 45, 48 and 49 would have been obvious at the time of our invention, in light of the five references cited by the Examiner. Reconsideration and withdrawal of this rejection is requested.

Having addressed all of the Examiner's outstanding concerns, it is believed that this application is in condition for allowance, and notice of such is earnestly solicited. No amendment made was related to the statutory requirements of patentability unless expressly stated herein, and no amendment made was for the purpose of narrowing the scope of any claim unless we argued above that such amendment was made to distinguish over a particular reference or combination of references.

If the Examiner has any questions or would like to make suggestions as to claim language, he is encouraged to contact Marlana K. Titus at (301) 762-8214.

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MARKED-UP VERSION OF THE CLAIMS AS AMENDED ABOVE

28. (Amended) A composition that confers protective immunity against Hantavirus infection, comprising

(c) an inert particle suitable for carrying a polynucleotide stably coated thereon, and

(d) a polynucleotide coated onto the particle, which polynucleotide comprises a promoter operative in a mammalian cell and a hantavirus M gene segment encoding a G1 glycoprotein and a G2 glycoprotein.